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LETTER

Additional evidence to support the role of a common variant near the complement factor I gene in susceptibility to age-related macular degeneration

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In 2008, Fagerness *et al*[1] provided new evidence of an association between common variants on chromosome 4q25 harboring the complement factor I gene and advanced age-related macular degeneration (AMD), a leading cause of irreversible blindness worldwide. Based on a high-density genotyping analysis and using a large sample (1228 case subjects and 825 control subjects of European descent), Fagerness *et al*[1] found the most significant evidence for association at a single-nucleotide polymorphism (SNP) located 2781 bp upstream of the 3′ UTR of the complement factor I gene (rs10033900). Until now, only one replication study has been done for this association in a Caucasian population of European ancestry, providing further support of this region's importance for AMD.[2] However, its relevance to other ethnic populations remains to be clarified, and evaluation of this association in cohorts of non-European ancestry is desired to establish the consistency and generalizability of the original association. We conducted a case–control association study to validate the reported association of the key variant, rs10033900, in a Japanese population.

We tested rs10033900 for its association with neovascular AMD, an advanced form of AMD, in a sample of 116 patients with neovascular AMD and in 189 controls. This same sample set was also used in our previous studies[3,4] and the phenotyping criteria have been fully described previously.[5] The demographics of the study population are presented in Table 1. It is important to note that this population has been previously verified to show no inflation of association statistics because of population stratification.[3,4] Genotyping was carried out using a predeveloped TaqMan SNP Genotyping Assay (Assay ID: C__34681305_10; Applied Biosystems, Foster City, CA, USA). We computed the following test statistics using SNPGWA v3.02 (http://www.phs.wfubmc.edu/public/bios/gene/downloads.cfm): a 2° of freedom genotypic association test; dominant, recessive, and additive genetic model tests (Cochran–Armitage trend test); a lack-of-fit test for the additive model; and the exact test for Hardy–Weinberg equilibrium (HWE).[6] The permutation procedure implemented in SNPGWA v3.02 was used with 100 000 iterations to obtain empirical *P*-values for all genotypic tests. The odds ratio and corresponding 95% confidence interval (CI) were calculated relative to the major allele. A pattern of risk associated with rs10033900 was assessed by logistic regression using R (http://www.r-project.org/), coding the rs10033900 genotype according to dominant, recessive, and additive models. We then used Akaike Information Criterion (AIC) to compare these genetic models.

No departure from HWE was observed at rs10033900 among the controls (P=0.45). We found statistically significant evidence for association between rs10033900 and neovascular AMD in our Japanese population (Table 2). The direction of association was consistent with the finding of Fagerness *et al*;[1] the minor 'C' allele of rs10033900 was associated with decreased disease risk (Table 2). Our result suggests that a recessive genetic model – with an odds ratio of 0.28 (95% CI, 0.11–0.69) for the rare homozygote CC (P=0.0035) – as the most parsimonious model (AIC=408.3, 399.7, and 404.7 for dominant, recessive, and additive models, respectively). The lack-of-fit test for the additive model was significant (P=0.043), indicating that its genotypic effect is deviated from additivity.

Our result shows, for the first time, the association of rs10033900 with AMD in a non-European population. A limitation of our study is the small sample size, but given the independent lines of evidence provided by previous studies,[1,2] our result is highly unlikely to be false positive. Our study provides additional evidence supporting the role of rs10033900 to AMD susceptibility, and also provides rationale for more detailed genetic characterization of the 4q25 region in Asian populations.

Table 1 Characteristics of the study population

	Neovascular AMD	*Controls*
Number of subjects	116	189
Gender (male/female)	91/25	114/75
Mean age ± SD (years)	75 ± 7.2	72 ± 5.8
Age range (years)	57–91	56–95

Abbreviations: AMD, age-related macular degeneration; SD, standard deviation.

Table 2 Allele and genotype distributions of rs10033900 and the results of association tests

	Summary statistics	
	Cases – no. (%)	*Controls – no. (%)*
Allele		
T	161 (69.0)	231 (61.0)
C	71 (31.0)	147 (39.0)
Genotype		
TT	51 (44.0)	73 (39.0)
CT	59 (51.0)	85 (45.0)
CC	6 (5.0)	31 (16.0)
	Association analyses	
Model	*Odds ratio (95% CI)*	*P-value (empirical P-value)*
Additive	0.68 (0.48–0.98)	0.036 (0.035)
Genotype (2 df)	OR_{het}: 0.99 (0.61–1.62)	0.014 (0.014)
	OR_{hom}: 0.28 (0.11–0.71)	
Dominant (1 df)	0.80 (0.50–1.28)	0.36 (0.34)
Recessive (1 df)	0.28 (0.11–0.69)	0.0035 (0.0022)

Abbreviations: df, degree of freedom; CI, confidence interval; OR_{het} and OR_{hom}, odds ratio for heterozygote and rare homozygote, respectively, estimated by unconditional logistic regression.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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